

Contributions of multiple inert gas elimination technique to pulmonary medicine · 3

Series editor: R Rodriguez-Roisin

Bronchial asthma

Robert Rodriguez-Roisin, Josep Roca

Historical background

In 1967 two Australian chest physicians drew attention to the importance of arterial blood gas abnormalities in 12 patients with status asthmaticus (acute severe asthma) and in 64 others with clinically less severe disease.¹ They documented that in many patients with asthma arterial blood gas abnormalities were commonly present, usually mild to moderate hypoxaemia. Likewise they outlined that, even when this fall in PaO_2 was insufficient to induce life threatening hypoxaemia, it rendered patients more vulnerable to effects from any further increase in airways obstruction. Even though there was a correlation between the reduction in forced expiratory volume in one

second (FEV_1) and the extent of arterial blood gas abnormalities, FEV_1 levels >1.0 litres were not a reliable predictor of the PaO_2 . One year later McFadden and Lyons² confirmed these results in 101 patients suffering an acute exacerbation of asthma, in whom arterial hypoxaemia was present in most; hypercapnia was less common and not observed until airway obstruction became severe. Subsequently McFadden *et al*³ postulated that obstructive changes in peripheral airways could be a factor that might explain why patients with acute severe asthma show refractoriness to standard treatment with bronchodilators or relapse after hospital discharge, or both. In all these studies the most likely mechanism of arterial

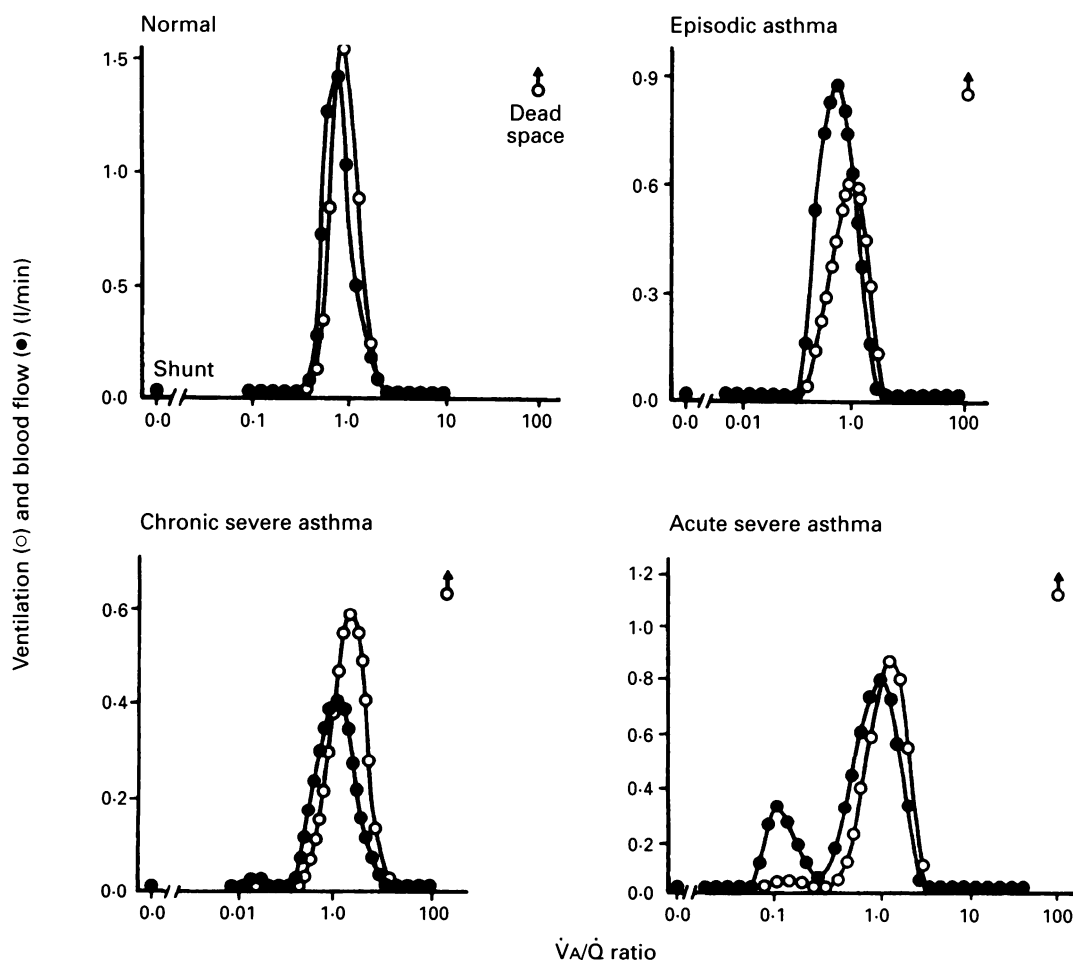


Figure 1 Different patterns of \dot{V}_A/\dot{Q} ratio distributions (ventilation (○) and blood flow (●)) plotted against a \dot{V}_A/\dot{Q} ratio on a log scale. Healthy young individuals have narrowly unimodal, well centred, distributions; in contrast, patients with episodic or chronic severe asthma display broadly unimodal distributions whereas those with acute severe asthma (irrespective of the use of mechanical ventilation) develop a predominant bimodal pattern of the blood flow distribution. Shunt (left ●) is absent and dead space (right ○) is normal in each condition.

Servei de Pneumologia
i Al·lèrgia
Respiratòria, Hospital
Clínic, Facultat de
Medicina, Universitat
de Barcelona,
Barcelona, Spain
R Rodriguez-Roisin
J Roca

Reprint requests to:
Dr R Rodriguez-Roisin.

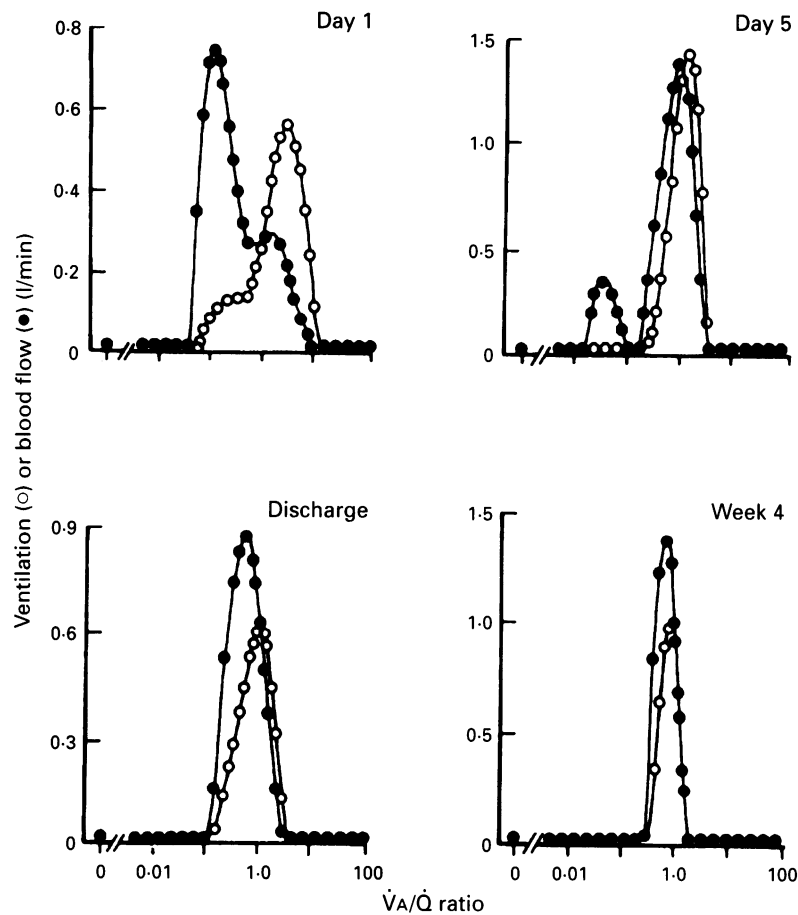


Figure 2 Sequential \dot{V}_A/\dot{Q} ratio distributions in a representative patient with acute severe asthma in hospital (days 1 and 5), at discharge, and one month thereafter. The characteristic bimodal blood flow pattern shown at day 1 was still present, although more modestly, at day 5, to become broadly unimodal at discharge. One month later both distributions were narrowly unimodal, similar to a healthy individual. Shunt (●) was always absent and dead space (not shown) was normal. Reproduced from ref 15 with permission.

hypoxaemia was considered to be ventilation-perfusion (\dot{V}_A/\dot{Q}) abnormalities, attributed mainly to an increased physiological dead space, although an additional small shunt effect was evident among the most affected patients. All in all, despite the general acknowledgement that \dot{V}_A/\dot{Q} inequality was the major cause of hypoxaemia, little information had been collected on the \dot{V}_A/\dot{Q} relationships in patients with asthma and their modification by different interventions.

Over the last 15 years a large body of evidence on pulmonary gas exchange in bronchial asthma has been collected using the multiple inert gas elimination technique (MIGET).^{4,5} This article reviews the characteristics of the principal mechanisms of pulmonary gas exchange in the different clinical forms of bronchial asthma in adults and their potential relation with structural changes. The effects of breathing high oxygen concentrations and the response to some of the current bronchodilator agents will also be discussed to shed further light on the mechanisms of abnormal gas exchange in asthma. This may help the clinician in the interpretation of the complex interplay between the intrapulmonary (essentially \dot{V}_A/\dot{Q} mismatching) and extrapulmonary (overall ventilation, cardiac output, and oxygen consumption) factors modulating arterial blood gases (P_{aO_2} and P_{aCO_2}) in one of the most common chronic pulmonary disorders.⁶

Mechanisms of arterial hypoxaemia

EPISODIC (INTERMITTENT) AND MILD TO MODERATE ASTHMA (fig 1)

The original study using MIGET was by Wagner *et al*⁷ in asymptomatic patients with long standing mild to moderate asthma, none having required medical attention for at least one month before the study. All but one patient had a normal or slightly reduced P_{aO_2} . The most novel finding was the presence of a clear-cut bimodal pattern in the blood flow distribution, with shunt and areas of high \dot{V}_A/\dot{Q} ratios conspicuously absent or trivial, and a normal dead space. This bimodal blood flow pattern included a large fraction of cardiac output associated with the mode of reduced \dot{V}_A/\dot{Q} regions, in which ventilation is decreased but perfusion remains unaffected. The extent of \dot{V}_A/\dot{Q} inequality and the prevalence of the bimodal blood flow pattern was greater in this early study than in later series studying patients with mild to moderate asthma.⁸⁻¹¹ Several reasons, including differences in patient selection, their clinical management and treatment, could have accounted for the apparent conflict between the first study⁷ and those that showed less \dot{V}_A/\dot{Q} mismatch, despite similar airways obstruction.⁸⁻¹¹

In one of the studies Wagner *et al*⁸ assessed the prevalence and variability of \dot{V}_A/\dot{Q} distributions in stable, symptomatic patients (mean FEV_1 72% predicted) once a week for two months. The patients were taking regular

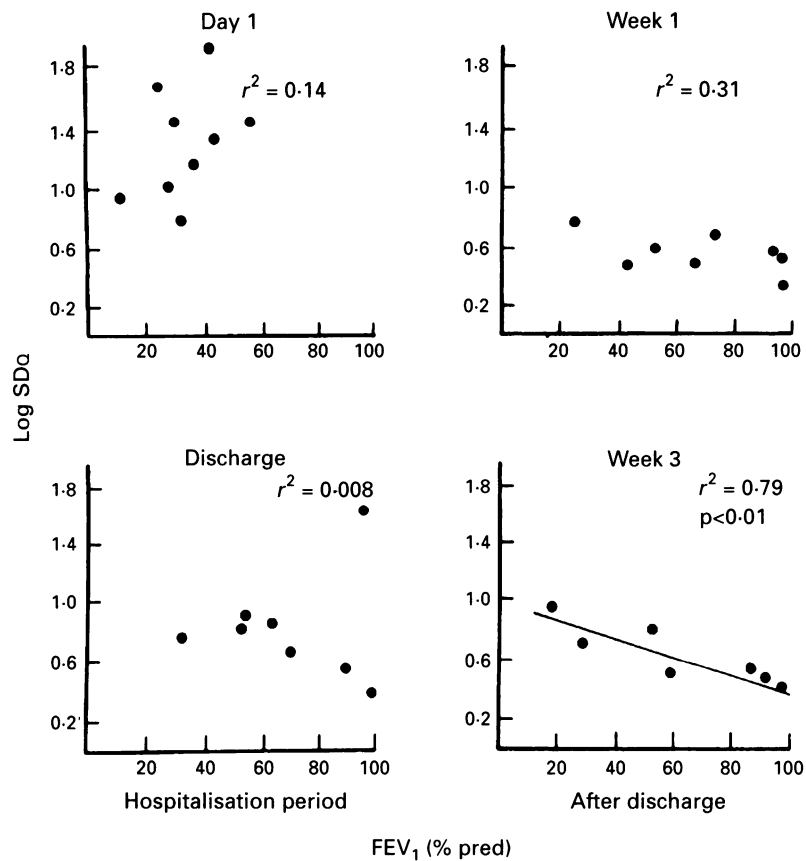


Figure 3 FEV_1 (% predicted) and gas exchange (expressed as the dispersion of blood flow, log SDQ) at day 1 of hospitalisation, at discharge, and at weeks 1 and 3 thereafter in patients with acute severe asthma who were hospitalised (each data point represents a single patient). Except at week 3, all other correlations were very weak. Similar correlations were shown between other indices of airway obstruction and gas exchange measurements. This suggests a complete dissociation between spirometric values and gas exchange in asthma. Reproduced from ref 15 with permission.

bronchodilator therapy (oral theophylline with or without inhaled β_2 agonists) and were also on inhaled corticosteroids, and about one third required regular oral steroid treatment. Their \dot{V}_A/\dot{Q} inequality, expressed as the dispersion of blood flow (the second moment, log SDQ), was abnormal in every patient for at least two weeks; in contrast, the dispersion of alveolar ventilation (log SDV) was much less abnormal. Interestingly, the occurrence of the bimodal profile in the dispersion of blood flow that contains areas of both normal and low \dot{V}_A/\dot{Q} ratios was variable and present in only one third of all \dot{V}_A/\dot{Q} measurements.

The three other studies⁹⁻¹¹ carried out in patients with stable mild asthma (mean $FEV_1 > 90\%$ predicted; mean $P_{aO_2} > 10.7$ kPa) included patients with intermittent asthma, taking β_2 agonists on demand, as well as others with moderate disease on maintenance therapy with specific β agonists, with or without inhaled steroids or oral theophylline preparations, but not taking oral corticosteroids. While baseline \dot{V}_A/\dot{Q} distributions were mostly unimodal and very narrow, some displayed broader unimodal perfusion and ventilation or modest bimodal blood flow patterns. As with the former studies, shunt was absent or negligible with no areas with high \dot{V}_A/\dot{Q} regions, and dead space was normal.

CHRONIC SEVERE ASTHMA (fig 1)

In patients with stable, chronic severe asthma (FEV_1 range 33–63% predicted; $P_{aO_2} > 8.0$ kPa)

the \dot{V}_A/\dot{Q} distributions were broad and unimodal, without shunt or areas with low or high \dot{V}_A/\dot{Q} regions.^{12,13} The amount of \dot{V}_A/\dot{Q} inequality was modest, as assessed by both the log SDQ and the log SDV, and dead space was normal. Probably, these patients could maintain near normal P_{aO_2} values with relatively little \dot{V}_A/\dot{Q} inequality despite severe airways obstruction because peripheral airways may have had less inflammatory change or more active hypoxic pulmonary vasoconstriction, or both. These data contrast with those in patients with chronic obstructive pulmonary disease (COPD) and the same degree of severe airway narrowing in whom chronic hypoxaemia, with or without hypercapnia, is a common hallmark of the disease.¹⁴

ACUTE SEVERE ASTHMA (figs 1 and 2)

Patients with status asthmaticus have been studied using MIGET within hours of attendance in the emergency department.¹⁵⁻¹⁸ The status of pulmonary gas exchange in most of these patients was grossly abnormal: the more severe the attacks the worse the \dot{V}_A/\dot{Q} abnormalities. The \dot{V}_A/\dot{Q} distributions were, however, similar to changes seen in less severe asthma with a predominant bimodal blood flow pattern as the principal cause of hypoxaemia without areas of high \dot{V}_A/\dot{Q} regions or increased dead space (figs 1 and 2). In contrast, a large amount of blood flow was diverted to alveolar units with low, but still poorly ventilated, \dot{V}_A/\dot{Q} ratios, but shunt was absent or minimal.

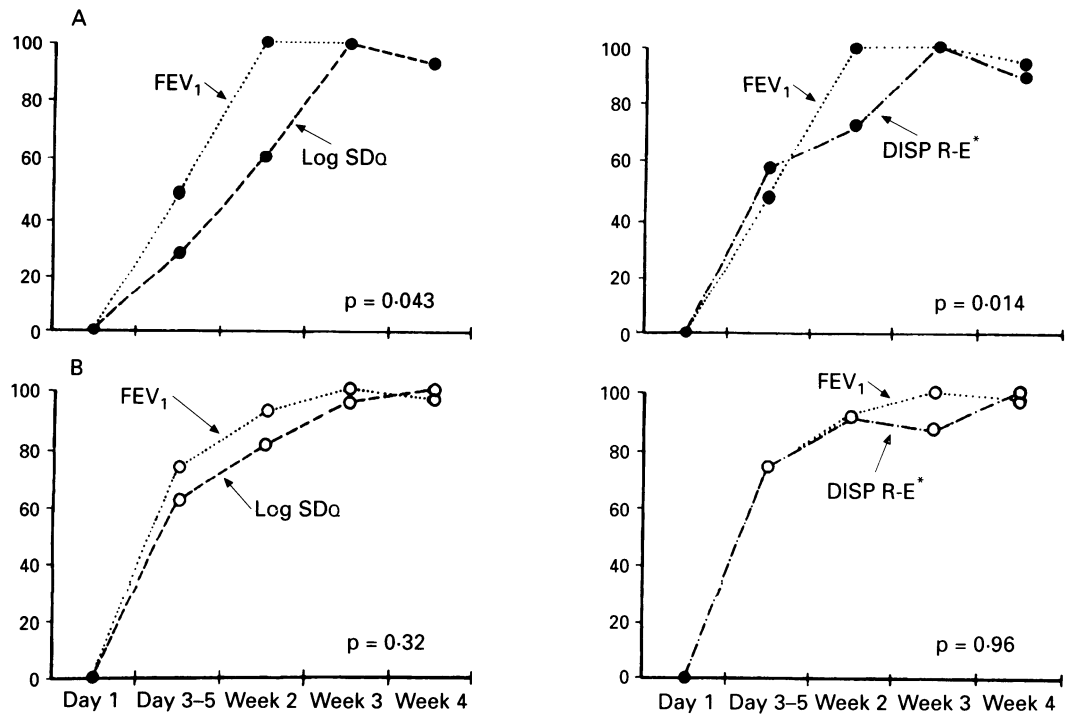


Figure 4 Time courses of improvement of FEV_1 and $\dot{V}A/\dot{Q}$ mismatch (as assessed by the dispersion of blood flow, $\log SDQ$) and a mathematical variable representing an overall index of $\dot{V}A/\dot{Q}$ heterogeneity ($DISP R-E^*$) in patients with acute severe asthma (A) in hospital or (B) discharged home. All variables are expressed in special units (100 arbitrary units were assigned to the differences between the least and the most abnormal value throughout the period of study; 0 corresponds to the measurements done in the emergency department). While in hospital patients approached their maximal improvement in FEV_1 at week 2, the two gas exchange indices were still only at 60% and 72% of their best value; in contrast, discharged patients displayed similar spirometric and gas exchange time courses without significant differences between them throughout the whole study period. Reproduced from ref. 17 with permission.

As expected, those patients attending the emergency department who were discharged because of a less severe attack had fewer $\dot{V}A/\dot{Q}$ abnormalities with recovery to normal $\dot{V}A/\dot{Q}$ distributions over a few days; in contrast, patients who required admission took about two weeks to recover.¹⁷

Patients with status asthmaticus needing mechanical support had the most abnormal pattern of the $\dot{V}A/\dot{Q}$ spectrum – that is, significantly bimodal blood flow profile.¹⁸ In these patients the high inspired oxygen concentrations which may prevent hypoxic pulmonary vasoconstriction, and the additional therapeutic effects of high doses of bronchodilators associated with potential vasodilation, may enhance the perfusion of low $\dot{V}A/\dot{Q}$ areas. In these critically ill patients the $\log SDQ$ was also more abnormal than the $\log SDV$, shunt was conspicuously small, and dead space was within normal limits.

Clinical relevance of $\dot{V}A/\dot{Q}$ abnormalities

In the studies described above there was no correlation between arterial blood gases and the indices of inert gas measurements. Only in two of the studies including patients with chronic moderate to severe asthma^{7,13} was $\log SDQ$ (one of the best descriptors of $\dot{V}A/\dot{Q}$ inequality) inversely correlated to PaO_2 with coefficient correlations above 0.75. The greater the $\dot{V}A/\dot{Q}$ mismatch the lower the PaO_2 , but baseline PaO_2 was generally high considering the extent of underlying $\dot{V}A/\dot{Q}$ heterogeneity measured in these patients. This relatively well preserved PaO_2 in the presence of different

degrees of $\dot{V}A/\dot{Q}$ mismatching could conceivably be attributed to the high levels of overall ventilation or cardiac output, or both, found in most studies. This observation highlights the major part played by these two extrapulmonary factors modulating PaO_2 , in addition to $\dot{V}A/\dot{Q}$ inequality, in some pulmonary diseases.⁶

Secondly, there was good agreement between predicted PaO_2 (reflecting the amount of $\dot{V}A/\dot{Q}$ mismatch according to MIGET) and measured PaO_2 , and no significant differences between the lines of identity and of regression, nor deviation from the line of identity.¹⁹ This suggests that diffusion equilibration of alveolar gas with end capillary blood is adequate for oxygen, even in the most critical life threatening forms of asthma.

Thirdly, and most important, irrespective of the severity of asthma there was a systematic lack of correlation between the measurements of airways obstruction and those of respiratory and inert gas exchange (fig 3).²⁰ This dissociation may reflect two different pathophysiological phenomena, suggesting that gas exchange abnormalities cannot be inferred from airflow obstruction in asthma. Indeed, a study of serial changes of $\dot{V}A/\dot{Q}$ inequalities and spirometric measurements in patients admitted with acute severe asthma showed that there were no significant interindividual correlations between maximal airflow rates and $\dot{V}A/\dot{Q}$ mismatch, either whilst in hospital or during the first two weeks after discharge.¹⁵ This suggests that spirometric changes predominantly reflect bronchoconstriction in larger and medium sized airways, while $\dot{V}A/\dot{Q}$ abnormalities are

mainly related to events occurring in the distal, small airways. A further study¹⁷ which assessed possible differences in the time course and severity of airway obstruction and \dot{V}_A/\dot{Q} inequality in patients with acute severe asthma according to whether admitted or discharged home reinforces this concept. As expected, on admission airflow rates and indices of gas exchange were significantly lower in those patients admitted than in those sent home. However, while in the former patients spirometric changes recovered more rapidly and efficiently than \dot{V}_A/\dot{Q} abnormalities, the time course of the two indices of lung function measurements in the latter group was similar (fig 4). From a pathophysiological viewpoint it can be postulated that patients sent home had fewer airway inflammatory changes and recovered more rapidly with treatment than those admitted, who in turn needed longer to recover their overall lung function. Lagerstrand *et al*²¹ have shown that \dot{V}_A/\dot{Q} abnormalities similar to those observed in human asthma can be clearly seen when small droplets of isotonic saline are nebulised in a rabbit model with no increase in total inspiratory resistance.

We have recently shown that, in patients with mild asthma²² and in healthy individuals,²³ the inhalation of platelet activating factor (PAF), a potent mediator of inflammation, provoked \dot{V}_A/\dot{Q} mismatch similar to that shown in patients with moderate to severe forms of asthma. It was suggested that these gas exchange abnormalities induced by PAF were more related to airway microvascular leakage than to bronchoconstriction by itself. These data would support the concept that endogenous release of PAF may be connected with the altered arterial blood gases shown during acute exacerbations of asthma.

Structure and functional correlations

Bronchial asthma is a disease in which active bronchoconstriction, together with airway inflammation, hyperaemia, inspissated mucus, mucus impaction, and bronchial wall oedema may all lead to the occlusion of peripheral airways.²⁴ The alveolar units distal to these narrowed airways may therefore be only minimally ventilated, even in severe acute attacks, by collateral pathways from relatively unaffected neighbouring alveoli, thus precluding the development of completely unventilated alveolar units (shunt). This obstruction produces areas of low \dot{V}_A/\dot{Q} regions that remain perfused but poorly ventilated. From a simple numerical viewpoint this must increase blood flow dispersion (log SDQ) more than ventilation dispersion (log SDV). Further, the presence of minimal or no shunt suggests that the occlusion of the airways is never functionally complete, and that the role of hypoxic pulmonary vasoconstriction is exceptionally efficient.

These features could account for the broadly unimodal or bimodal patterns of \dot{V}_A/\dot{Q} dependent on the clinical state of each patient. In chronic severe asthma it may be that the airway narrowing caused by inflammation occurs predominantly in the more distal airways

producing a broadly unimodal blood flow profile.^{12,13} In contrast, in acute severe asthma the inflammatory process may extend more centrally, resulting in a bimodal pattern of pulmonary perfusion.¹⁵⁻¹⁸

In postmortem lung studies from patients with sudden fatal asthma bronchioles were occluded, there was increase in thickness of the smooth muscle, and an inflammatory infiltrate with both mononuclear cells and eosinophils.²⁵ Although muscular pulmonary arteries adjacent to occluded and inflamed small airways did not show morphological features of chronic hypoxia, they did have considerable inflammatory changes in their walls which were most noticeable when close to peripheral airways. In spite of the fact that the precise functional significance of this vascular involvement still remains uncertain, the structural findings shown in peripheral airways in these patients support our contention that small airway occlusion constitutes the morphological basis of gas exchange abnormalities found in acute asthma.¹⁵⁻¹⁸

Effects of breathing oxygen

Given that \dot{V}_A/\dot{Q} mismatching is the principal determinant of the low P_{aO_2} in asthma, a clinical consequence of practical interest is that arterial hypoxaemia can be rapidly and efficiently reversed by moderate increases in inspired oxygen concentration – that is, between 0.24 and 0.40. When breathing 100% oxygen the effects of gas exchange remain similar irrespective of the clinical type of asthma. Specifically, \dot{V}_A/\dot{Q} mismatch substantially worsens: the index of blood flow dispersion (log SDQ) always increases significantly. This occurs both in patients with acute severe asthma^{16,18} and also in those with chronic severe asthma.^{12,13} Corte and Young¹² showed in a few patients with chronic asthma that the inert gas variables remained unaltered during oxygen breathing in those with more abnormal baseline \dot{V}_A/\dot{Q} distributions, suggesting that these patients had more distal airway involvement. An increase of the log SDQ, with or without the development of areas with poorly ventilated \dot{V}_A/\dot{Q} ratios, while breathing 100% oxygen suggests that hypoxic pulmonary vasoconstriction is reduced even in the absence of pulmonary haemodynamic changes.

In patients with status asthmaticus requiring mechanical support neither the pulmonary arterial pressure nor the cardiac output changed significantly when breathing 100% oxygen.¹⁸ At first glance this suggests the absence of a pulmonary vascular response to oxygen. Yet the log SDQ increased significantly. Using the mechanisms of vascular recruitment and dilatation, the pulmonary circulation may redistribute blood flow without altering standard flow-pressure relationships but still induces significant changes in some of the most common markers of \dot{V}_A/\dot{Q} inequalities. Similar data have been reported in patients with COPD^{26,27} or cryptogenic fibrosing alveolitis.²⁸

Furthermore, patients with critical life threatening status asthmaticus on mechanical sup-

port displayed an additional important finding: the development of moderate amounts of shunt (mean 8.3% of cardiac output) while breathing 100% oxygen,¹⁸ a rare finding in patients with chronic respiratory disease.¹⁴ Indeed, those with acute lung injury develop a significant increase in shunt (on average 30%) when breathing 100% oxygen.²⁹ The development of shunt could be explained by collateral ventilation becoming insufficient whilst breathing oxygen, causing collapse of alveolar units with critical inspiratory \dot{V}_A/\dot{Q} ratios³⁰ and, ultimately, reabsorption atelectasis. Similarly, the possibility that breathing oxygen relaxes the vascular tone of already completely unventilated (atelectatic) areas at baseline inspired oxygen conditions, thereby increasing the perfusion of these small pre-existing shunts, may be an additional factor to be considered. This would increase shunt without the need for further reabsorption atelectasis.

In contrast, the effects of 100% oxygen on the log SDv were less uniform than those observed on the log SDQ. Thus, while the former variable increased (worsened) significantly in patients with acute severe asthma breathing spontaneously¹⁶ or remained unaltered in chronic severe asthma,¹³ it decreased (improved) in patients with status asthmaticus requiring mechanical ventilation.¹⁸ Although changes in one distribution may influence the other, the mechanisms underlying log SDv changes after breathing oxygen remain uncertain.

It is known that breathing 100% oxygen decreases airways resistance and improves maximal airflow rates in patients with COPD³¹ and mitigates bronchial hyperresponsiveness in patients with asthma.³² Accordingly, oxygen breathing should improve \dot{V}_A/\dot{Q} mismatch by reducing the amount of low \dot{V}_A/\dot{Q} ratios, thus decreasing the log SDQ. In principle, hyperoxic bronchodilatation in the presence of widespread airway disease could reduce airways resistance in hypoxic areas and increase local blood flow, thus partly ablating hypoxic pulmonary vasoconstriction. This would tend to improve the function of the lung as a gas exchanger, other factors being equal.

Gas exchange response to bronchodilators

Bronchodilators are one of the mainstays of the current therapeutic strategy in asthma.³³ In patients with acute severe asthma a total dose of 600 μg inhaled salbutamol did not induce further \dot{V}_A/\dot{Q} worsening¹⁶ while FEV₁ improved substantially (by 50%). Similar results, although with a smaller bronchodilator effect (35% increase in FEV₁), were observed in patients with chronic severe asthma after 300 μg inhaled salbutamol.¹³ In a double blind, placebo controlled study in patients with acute asthma, intravenous aminophylline given at therapeutic doses caused only minor changes in ventilation, respiratory rate, cardiac output, oxygen consumption, and \dot{V}_A/\dot{Q} inequality, together with a significant but small increase in

FEV₁ (mean 17%).³⁴ Similar results using the same doses have been recorded for patients with COPD whilst recovering from an acute exacerbation.²⁷ By contrast, the administration of intravenous salbutamol (4 $\mu\text{g}/\text{min}$, total dose 360 μg) in patients with acute asthma aggravated \dot{V}_A/\dot{Q} mismatch (log SDQ increased) while inducing a similar degree of airway bronchodilatation to inhaled salbutamol; heart rate, cardiac output, and oxygen uptake also increased substantially.¹⁶ We have suggested that both nebulised salbutamol and adrenaline in a canine model of asthma upset pulmonary gas exchange less than isoprenaline.³⁵ Although it is not possible to differentiate between an increase in cardiac output causing an increase in the dispersion of blood flow or a reduction in the pulmonary vascular tone, or both, it seems reasonable to ascribe the further \dot{V}_A/\dot{Q} deterioration following intravenous salbutamol to the relevant associated cardiovascular and metabolic effects of the drug, probably due to higher plasma levels. In an experimental model of bronchoconstriction after methacholine Wagner *et al*³⁶ have suggested that aggravation of \dot{V}_A/\dot{Q} relationships with an increase in cardiac output depends more on the pulmonary vascular tone of uninjured areas than on those regions with \dot{V}_A/\dot{Q} mismatching.

Further worsening or lack of improvement in \dot{V}_A/\dot{Q} mismatch after airflow rates have returned to normal following bronchodilators is one of the most provocative findings ever seen in asthma. However, this observation concurs with our hypothesis that \dot{V}_A/\dot{Q} mismatch in asthma is related more to abnormalities in peripheral airways, and airflow rates essentially reflect more central airways obstruction.¹⁵⁻¹⁷

From a clinical viewpoint, however, some conclusions can be drawn. Although hypoxaemia associated with the use of bronchodilators at therapeutic levels does not seem to represent a serious side effect, clinicians should (1) be aware that hypoxaemia may occur after use of bronchodilators depending on the dose and mode of administration and the clinical characteristics of each patient; (2) realise that substantial \dot{V}_A/\dot{Q} mismatching may occur with little change, if any, in Pao₂, and (3) remember that changes in total ventilation, cardiac output, and oxygen consumption may play a pivotal part in determining overall gas exchange, quite separate from those due to inspired oxygen concentration by itself.

Supported by grants FIS (Fondo de Investigación Sanitaria) 91/0290 and 93/0306 de la Seguridad Social.

- 1 Tai E, Read J. Blood-gas tensions in bronchial asthma. *Lancet* 1967;i:644-6.
- 2 McFadden ER Jr, Lyons HA. Arterial blood gas tensions in asthma. *N Engl J Med* 1968;278:1027-32.
- 3 McFadden ER Jr, Kiser R, DeGroot WJ. Acute bronchial asthma. Relationships between clinical and physiologic manifestations. *N Engl J Med* 1973;288:221-5.
- 4 Wagner PD, Saltzman HA, West JB. Measurement of continuous distributions of ventilation-perfusion ratios: theory. *J Appl Physiol* 1974;36:588-99.
- 5 Evans JW, Wagner PG. Limits on \dot{V}_A/\dot{Q} distributions from analysis of experimental inert gas elimination. *J Appl Physiol* 1977;42:889-98.
- 6 Rodríguez-Roisin R, Wagner PD. Clinical relevance of ventilation-perfusion inequality determined by inert gas elimination. *Eur Respir J* 1990;3:469-82.
- 7 Wagner PD, Dantzker DR, Iacovoni VE, Tomlin WC, West

- JB. Ventilation-perfusion inequality in asymptomatic asthma. *Am Rev Respir Dis* 1978;118:511-24.
- 8 Wagner PD, Hedenstierna G, Bylin G. Ventilation-perfusion inequality in chronic asthma. *Am Rev Respir Dis* 1987;136:605-12.
 - 9 Young IH, Corte P, Schoeffel RE. Pattern and time course of ventilation-perfusion inequality in exercise-induced asthma. *Am Rev Respir Dis* 1982;125:304-11.
 - 10 Rodriguez-Roisin R, Ferrer A, Navajas D, AGN Agusti, Wagner PD, Roca J. Ventilation-perfusion mismatch after methacholine challenge in patients with mild bronchial asthma. *Am Rev Respir Dis* 1991;144:88-94.
 - 11 Lagerstrand L, Larsson K, Ihre E, Zetterström O, Hedenstierna G. Pulmonary gas exchange following allergen challenge in patients with allergic asthma. *Eur Respir J* 1992;5:1176-83.
 - 12 Corte P, Young I. Ventilation-perfusion relationships in symptomatic asthma. Response to oxygen and clemastine. *Chest* 1985;88:167-5.
 - 13 Ballester E, Roca J, Ramis LL, Wagner PD, Rodriguez-Roisin R. Pulmonary gas exchange in chronic asthma. Response to 100% oxygen and salbutamol. *Am Rev Respir Dis* 1990;141:558-62.
 - 14 Agusti AGN, Barberà JA. Contribution of multiple inert gas elimination technique to pulmonary medicine: 2 - Chronic pulmonary diseases: chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Thorax* 1994;49:924-32.
 - 15 Roca J, Ramis LL, Rodriguez-Roisin R, Ballester E, Montserrat JM, Wagner PD. Serial relationships between ventilation-perfusion inequality and spirometry in acute severe asthma requiring hospitalization. *Am Rev Respir Dis* 1988;137:1055-61.
 - 16 Ballester E, Reyes A, Roca J, Guitart R, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. *Thorax* 1989;44:258-67.
 - 17 Ferrer A, Roca J, Wagner PD, Lopez FA, Rodriguez-Roisin R. Airway obstruction and ventilation-perfusion relationships in acute severe asthma. *Am Rev Respir Dis* 1993;147:579-84.
 - 18 Rodriguez-Roisin R, Ballester E, Roca J, Torres A, Wagner PD. Mechanisms of hypoxemia in patients with status asthmaticus requiring mechanical ventilation. *Am Rev Respir Dis* 1989;139:732-9.
 - 19 Roca J, Wagner PD. Contribution of multiple inert gas elimination technique to pulmonary medicine: 1 - Principles and information content of the multiple inert gas elimination technique. *Thorax* 1994;49:815-24.
 - 20 Wagner PD, Rodriguez-Roisin R. Clinical advances in pulmonary gas exchange. *Am Rev Respir Dis* 1991;143:883-8.
 - 21 Lagerstrand L, Dahlbäck M, Hedenstierna G. Gas exchange during simulated airway secretion in the anaesthetized rabbit. *Eur Respir J* 1992;5:1215-22.
 - 22 Félez MA, Roca J, Barberà JA, Santos C, Rotger M, Fan Chung K, et al. Inhaled platelet activating factor worsens gas exchange in mild asthma. *Am J Respir Crit Care Med* 1994;150:369-73.
 - 23 Rodriguez-Roisin R, Félez MA, Fan Chung K, Barberà JA, Wagner PD, Cobos A, et al. Platelet activating factor causes ventilation-perfusion mismatch in humans. *J Clin Invest* 1994;93:188-99.
 - 24 Hogg JC. Varieties of airway narrowing in severe and fatal asthma. *J Allergy Clin Immunol* 1987;80 (Suppl Part 2):417-9.
 - 25 Saetta M, Di Stefano A, Rosina C, Thiene G, Fabbri LM. Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma. *Am Rev Respir Dis* 1991;143:138-43.
 - 26 Torres A, Reyes A, Roca J, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in chronic obstructive pulmonary disease during ventilator weaning. *Am Rev Respir Dis* 1989;140:1246-50.
 - 27 Barberà JA, Reyes A, Roca J, Montserrat JM, Wagner PD, Rodriguez-Roisin R. Effect of intravenously administered aminophylline on ventilation/perfusion inequality during recovery from exacerbations of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992;145:1328-33.
 - 28 Agusti AGN, Roca J, Gea J, Wagner PD, Xaubet A, Rodriguez-Roisin R. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1991;143:219-25.
 - 29 Santos C, Roca J, Torres A, Cardús J, Barberà JA, Rodriguez-Roisin R. Patients with acute respiratory failure increase shunt during 100% O₂ breathing (abstract). *Eur Respir J* 1992;5 (Suppl 15):272s.
 - 30 Dantzker DR, Wagner PD, West JB. Instability of lung units with low \dot{V}_A/\dot{Q} ratios during O₂ breathing. *J Appl Physiol* 1975;38:886-95.
 - 31 Astin TW. The relationships between arterial blood oxygen saturation, carbon dioxide tension, and pH and airway resistance during 30 percent oxygen breathing in patients with chronic bronchitis with airway obstruction. *Am Rev Respir Dis* 1970;102:382-7.
 - 32 Inoue H, Inoue C, Okayama M, Sekizawa K, Hida W, Takishima Y. Breathing 30 per cent oxygen attenuates bronchial responsiveness to methacholine in asthmatic patients. *Eur Respir J* 1989;2:506-12.
 - 33 NHLB Institute, NIH. International consensus report on diagnosis and treatment of asthma. *Eur Respir J* 1992;5:601-41.
 - 34 Félez MA, Montserrat JM, Viegas CA, Roca J, Wagner PD, Rodriguez-Roisin R. Effect of intravenous aminophylline on pulmonary gas exchange during acute severe asthma (abstract). *Eur Respir J* 1991;4 (Suppl 14):224s.
 - 35 Rodriguez-Roisin R, Bencowitz HZ, Ziegler MG, Wagner PD. Gas exchange responses to bronchodilators following methacholine challenge in dogs. *Am Rev Respir Dis* 1984;130:617-26.
 - 36 Wagner PD, Schaffartzik W, Prediletto R, Knight DR. Relationship among cardiac output, shunt, and inspired O₂ concentration. *J Appl Physiol* 1991;71:2191-7.